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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,533	05/26/2005	David J. Waxman	701586-52522	1019

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
10/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/509,533	WAXMAN ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 October 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *20 October 2008*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: See *Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,3-18,31-33,37 and 38*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/QUANG NGUYEN, Ph.D./
Primary Examiner, Art Unit 1633

Continuation of 3. NOTE: The scope of proposed amended claim 37 is not the same as that of finally rejected claim 37, and therefore it would have required further consideration and/or search.

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's arguments are respectfully not found persuasive to overcome the rejections of record for reasons discussed below.

1. With respect to the rejection under 35 USC 103(a) over Waxman et al and Bilbao et al., once again Applicant argues that the Examiner ignored the Declaration of Dr. Waxman in which Dr. Waxman explained that using an apoptosis inhibiting agent in connection with cancer therapy would have gone against the conventional wisdom and evidenced by two review articles in Exhibits A and B; and that none of the secondary references of Bilbao, Robertson and Beidler is directed to cancer treatment. Applicant also argues that a skilled artisan would not have been motivated to combine the cited references because a skilled artisan would not apply agents that would appear to result in decreased apoptosis to cancer patients in whom inducing cell death is the usual goal. Applicant further argues that it was unexpected that tumor cells expressing the prodrug-acivating P450 enzyme together with an anti-apoptotic factor would eventually die following prodrug treatment, indicating that the activated prodrug is eventually able to circumvent the anti-apototic factor and kill the cancer cells by a slower, alternative non-apoptotic mechanism. Finally, Applicant argues that the Bilbao reference does not state or even imply that Bcl2 may be useful in enhancing toxin gene therapy for cancer cell treatment.

Firstly, it should be noted that the rejections of record do not teach or even suggest the sole use of an apoptosis inhibiting agent to treat cancer that would have gone against the conventional wisdom and review articles in Exhibits A and B. The primary reference clearly teaches that some therapeutic enhancement may be anticipated in tumor cells with high levels of endogenous RED expression (page 55, lines 11-13), and the importance of bystander cytotoxicity resulting when active drug metabolites diffuse or otherwise transferred from their site of generation within a transduced tumor cell to a neighboring, naïve tumor cell and leading to significant tumor regression even when a minority of tumor cell is transduced with the prodrug activation gene (page 3, liens 15-28). As already set forth in the rejection of record, an ordinary skilled artisan would modify the teachings of Waxman et al by further comprising the step of transducing neoplastic cells already transduced wih both P450/RED genes with a vector encoding an apoptosis inhibiting agent, such as Bcl-2 (transient and/or regulated expression), in light of the teachings of Bilbao et al. An ordinary skilled artsian would have been motivated to carry out such modification in order to achieve maximal intratumoral chemotherapeutic drug activation via enhanced expression levels of both P45/RED genes and/or a transient delayed in the death of tumor cells already transduced with both P450/RED genes by an apoptosis inhibiting agent would generate a prolonged and higher concentration of cytotoxic drug metabolites to neighboring native tumor cells resulting in a bystander cytotoxicity which is recognized to lead to significant tumor regression. Bilbao et al already demonstrated succesfully a method to prolong or enhance transgene expression (up to 2 log increase), including a therapeutic gene transgene; and stated explicitly "Strategies to prolong the expresssion of transgene delivered by adenovirus vector, even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical utility".

Secondly, there is nothing that is unexpected or surprising that tumor cells expressing the prodrug-activating P450 enzyme together with an anti-apoptotic factor would eventually die following prodrug treatment. This is because the primary reference of Waxman et al already demonstrated killing neoplastic cells in a mammalian patient using RED gene transfer in combination with cytochrome P450 gene transfer for enhancing the sensitivity of neoplastic cells to anti-cancer drugs that are activated by P450 enzymes; and that at least neoplastc cells such as breast cancer cells or prostate cancer cells are known to express endogenous antiapoptotic proteins such as Bcl-2 as evidenced by the reviews in Exhibits A and B.

Thirdly, Bilabo et al. stated explicitly "Strategies to prolong the expresssion of transgene delivered by adenovirus vector, even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical utility". The transgene in the statement encompasses any transgene, including any therapeutic transgene such as a toxin transgene selectively delivered for expression in cancer cells to achieve their eradication as already recognized by Bilbao et al. (page 2, lines 15-27). Moreover, in addition to the teachings of Bilbao et al, at the effective filing date of the present application the main concept of co-expressing an apoptosis-inhibiting agent to enhance the expression of a desired transgene was also taught by Luo et al and Wilson et al.

2. With respect to additional 103 rejections of record, Applicant argues basically that none of the additional cited references of Robertson et al., Griffith et al and Beidler et al provides the missing motivation to combine Waxman et al. with Bilbao et al.

Please refer to the Examiner's responses to Applicant's arguments on the deficiencies of the combination of Waxman et al and Bilbao et al in the preceding paragraphs. The use of additional cited references was used primarily to supplement the combined teachings of Waxman et al and Bilbao et al on additional limitations in dependent claims.